Review

Amyloidosis and renal disease in patients with Crohn's disease

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Abstract: Crohn's disease (CD) results from an aberrant immune response against commensal microbiota in genetically susceptible hosts. However, the nature of immune defects, the microflora involved, and genetic susceptibility remain incompletely defined and controversial. This review seeks to describe the present state of association between CD and renal disease; moreover, we highlight the convergence of CD with amyloidosis that can trigger sustained inflammation, producing the pathological alteration observed in both diseases. The following MESH terms were searched in PubMed, PubMed Central (PMC), and Web of Science: "Crohn´s disease" and "renal disease." The R RISmed package was used for PubMed and PMC. The abnormal humoral immune response is described along with alterations in immune cell migration mechanisms in CD during inflammation.
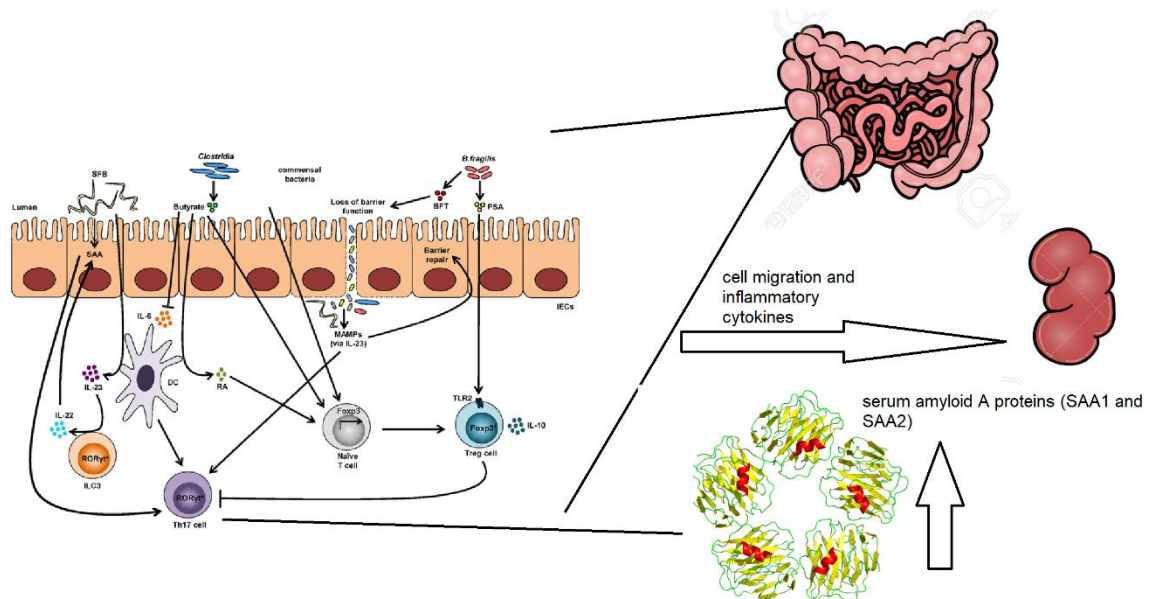
Keywords: Crohn's disease; renal disease; amyloidosis

1. Introduction

Crohn's disease (CD) is a relapsing systemic inflammatory disease that mainly affects the gastrointestinal tract with extraintestinal manifestations and is associated immune disorders. Genome-wide association studies have identified susceptibility loci that—triggered by environmental factors—lead to disturbed innate (i.e., disturbed intestinal barrier, Paneth cell dysfunction, endoplasmic reticulum stress, defective unfolded protein response and autophagy, impaired recognition of microbes by pattern recognition receptors such as nucleotide-binding domain and Toll-like receptors on dendritic cells and macrophages) and adaptive (i.e., imbalance of effector and regulatory T cells and cytokines, migration and retention of leukocytes) immune responses to a diminished diversity of commensal microbiota [1].

Among the pathological manifestations of CD, the formation of kidney stones is usually more common in affected individuals than in the general population. The frequency of lithiasis in this group of patients is estimated to be 12%–28% [2]. Most of these stones comprise calcium oxalate (CaOx), which has commonly been attributed to the presence of high urinary oxalate output accompanying fat and bile salt malabsorption. Factors other than urinary supersaturation with CaOx have also been implicated in stone development, e.g., low levels of the antilithogenic agents, magnesium, and citrate[3], [4]. However, despite their tendency to develop hyperoxaluria, hypocitraturia, hypomagnesuria, and hypophosphaturia and have low urine volume[5], most patients with CD do not develop renal stones, and factors determining an individual's risk of developing these stones remain unclear[6] . It is an increasing urological disorder of human health, affecting about 12% of the world population[7].

Additionally, the presence of amyloidosis has been described in patients with CD; it is characterized by reactivity in the acute phase that appears during sustained inflammation, similar to that observed in tumors, infectious diseases (tuberculosis, familial Mediterranean fever, bronchiectasis, osteomyelitis, etc.), and chronic inflammatory diseases (mainly rheumatic but inflammatory bowel disease [IBD] as well). Amyloidosis is a rare but serious complication of IBD, being more frequent in patients with CD than in those with ulcerative colitis (UC)[8].

This review seeks to describe the present state of association between CD and renal disease; moreover, we highlight the convergence of CD with amyloidosis that can trigger the sustained inflammation that may explain the pathological alteration observed in both diseases.

2. Materials and Methods

Searches were performed in PubMed, PubMed Central (PMC), and Web of Science using the following MESH search terms: "Crohn´s disease" and "renal disease." For PubMed and PMC, the R RISmed package was used [9]. Systematic searches were performed according to PRISMA criteria, obtaining 1002 records (from 2009 to 2019). The advanced search tool was used for Web of Science (using the Boolean operator AND among the previously mentioned terms, obtaining 415 records, from 2009 to 2019). Then the relevance of all records was evaluated according to the title and summary. If considered relevant, the entire article was examined, and 51 articles were selected using this method.

2.1. Histopathological spectrum of renal biopsies in patients with Crohn's syndrome

Renal disease is a complication of IBD, including CD and UC; renal and genitourinary involvement has been reported in 4%–23% of patients with CD [10]manifesting primarily as urinary stones, fistulas, and renal tubular damage. Parenchymal renal disease is rare but has been well documented in global literature as case reports describing glomerulonephritis (GN)[6].

In patients with CD, the most common indication for renal biopsy was acute or chronic kidney failure (63% [52 of 83]) and nephrotic-range proteinuria (16% [13 of 83]). IgA nephropathy (IgAN) was the most common diagnosis (24% [20 of 83]), followed by interstitial nephritis (19% [16 of 83]), arterionephrosclerosis (12% [10 of 83]), acute tubular injury (8% [7 of 83]), proliferative GN (7% [6 of 83]), and minimal change disease (5% [4 of 83]) [11].

The frequency of IgAN in specimens of patients with IBD was significantly higher than that in all other native renal biopsy specimens from the same period (24% [20 of 83] versus 8% [2734 of 33,630]; P < 0.001) [11].
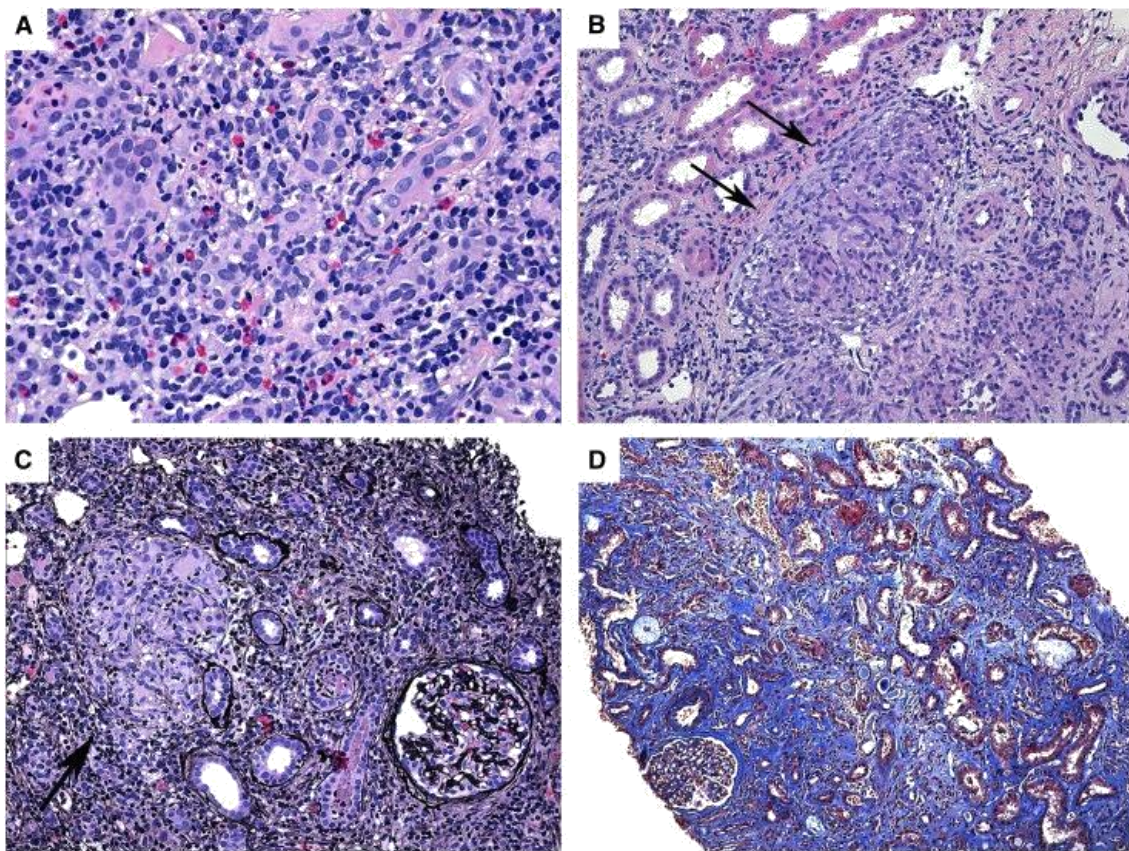
Figure 1. Pathological features of interstitial nephritis associated with inflammatory bowel disease: (**a**) Acute interstitial nephritis with dense interstitial inflammation predominantly comprising lymphocytes and eosinophils (hematoxylin and eosin, original magnification ×200); (**b** and **c**) Granulomatous interstitial nephritis with interstitial infiltration by mononuclear cells and noncaseating granulomas with multinucleated giant cells (arrows) (hematoxylin and eosin, Jones methenamine silver, both original magnification ×200); (**d**) Chronic interstitial nephritis with diffuse interstitial fibrosis and tubular atrophy; the glomerulus is preserved (Masson trichrome, original magnification ×100) modified from [11].

In summary, CD is associated with a spectrum of renal complications likely related to chronic inflammation or drug therapy in these patients. Additionally, the most common diagnosis on renal biopsy is IgA nephropathy, and its significantly higher prevalence in patients with CD suggests a shared pathophysiology between the intestinal and renal disease.

Interstitial nephritis is the second most common diagnosis, which is often, although not always, associated with amino salicylate therapy. In general, a high degree of clinical suspicion is needed for the early diagnosis and prevention of these renal complications of CD[11].

2.2. MicroRNAs in patients with Crohn's disease who develop renal disease

Emerging evidence suggests that microRNA (miRNA)-mediated gene regulation influences various autoimmune disease processes, including CD, but the biological function of miRNAs in CD remains debatable. miRNAs are a group of endogenous, small, noncoding RNAs approximately 22 nucleotides in length that regulate gene expression by binding to the noncoding region (3-UTR) of target mRNA molecules at the posttranscriptional level. Interestingly [12], there is compelling

evidence that a range of miRNAs are involved in the regulation of immunity, including the development and differentiation of immune cells, and the release of inflammatory mediators. miRNAs are differentially expressed in the serum and mucosa of patients with CD, suggesting that miRNA deregulation can play an important role in the development of CD [12].

miR-141 is aberrantly expressed in two other autoimmune diseases (lupus and psoriasis) [10]. It has been reported that several factors, such as Wnt signaling, DNA methylation, and miRNAs, contribute to the regulation of The chemokine (C-X-C motif) ligand (CXCL); however, the mechanism that promotes CXCL expression during intestinal inflammation remains unclear [11].

Based on the fact that CXCL12β levels significantly increase in CD and that miR-141 shows a significant reduction of expression in the same cell type, we assume that miR-141 targeting the CXCL12β pathway in CD serves as an important mechanism to regulate the colonic expression of CXCL12β/CXCL12-controlled immune cell trafficking in the experimental models of colitis and the process of CD dysfunction in humans[13].

Additionally, it has been shown that miR-141-mediated immune cell trafficking via CXCL12β in CD plays a key role in gastrointestinal tract inflammation [13].

2.3. Interleukin-17 and T helper 17 cells in patients with CD with renal disease

Interleukin-17 (IL-17) plays a central role in immune regulation, and T helper 17 (Th17) cells are associated with chronic inflammatory diseases. The Th17 subset generally produces interleukin-17A, which, in the experimental models of organ-specific autoimmune inflammation, plays an important role in CD [14].

CD is an IBD that affects specific locations in the gastrointestinal tract, and when inflammation occurs at different locations, it is known as UC [15].

In both diseases, local inflammation in the mucosa leads to the destruction of the lamina, causing complications such as perforations and internal or external fistulas [16].

Inflammatory manifestations in joints other than those observed in rheumatoid arthritis (RA) can be a part of spondyloarthropathies. As in RA and psoriasis, the contribution of tumor necrosis factor (TNF) has been demonstrated in a significant proportion of patients with IBD by the positive effect of TNF inhibition [16].

A clinical study using endoscopic biopsies has reported that the cytokines IL-23 and IL-17 as well as IL-12 are overexpressed in CD lesions [17].

However, CD and UC may be pathogenetically different. Some studies have found differences in cytokine expression because IL-17 is more strongly associated with UC and interferon-γ with CD [17].

Additionally, the secretion of IL-17A, as well as of IL-17F, IL-21, and IL-22, suggests that Th17 subset plays a crucial role as a pleiotropic proinflammatory Th subset.

There is experimental evidence to support the notion that Th1 and Th17 cells contribute to renal injury in renal inflammatory diseases like glomerulonephritis [18]. This suggests that the mechanisms of migration in Th1 and Th17 cells can be a problem for these patients, causing the inflammatory process to affect the kidneys.

2.4. Immune cell migration during inflammation in patients with Crohn's disease

The validity of the paradigm of immune cell migration in chronic diseases and the different organs affected by their deregulation is the key to understanding the association between CD and renal involvement [19]. On the other hand, patients with leukocyte adhesion deficiency syndrome have been observed to exhibit impaired leukocyte migration into tissues; this results in recurrent bacterial and fungal infections and peripheral leukocytosis due to defects at different stages in the multistep paradigm of leukocyte transit, including reduced expression of β2 integrins or fucosylated selectin ligands or an impaired ability to activate leukocyte integrins after chemokine stimulation [20]. Therefore, "experiments of nature" have provided a "proof of principle" that the transit of

molecules involved in the different steps of the multistep transit paradigm in humans contributes in unique ways to leukocyte transit i*n vivo* [21].

Natalizumab, a monoclonal antibody targeting the α4 integrin chain that blocks the binding of α4β1 (VLA-4) to VCAM-1 in Th1 cells (Th1 cell infiltration in the brain is mediated by the binding of α4β7 to CAM-1, with a very similar process occurring in the Th1cell infiltration in the intestines), has been successfully used in the treatment of multiple sclerosis and CD [20]. This clinical success has established the "proof of principle" that specifically interfering with the transit of leukocytes to the tissue is a new effective therapeutic strategy.

However, specific complications in infectious diseases that led to the withdrawal of this promising therapy emphasize the need for a greater understanding of the host defense components mediated by the subsets of specific leukocytes and specific transit molecules, as well as the need for finding more precise and specific leukocyte inhibitors transiting cellular subsets [22].

The host response to an infection or acute injury comprises a robust neutrophilic inflammatory response [22]. As is often the case in inflammation, this is a "double-edged sword," and this robust protective response can also be detrimental to the host tissue as host response to many acute tissue attacks, such as ischemia followed by reperfusion, induces a neutrophil-rich inflammatory response that substantially contributes to tissue injury [23]. Ischemia–reperfusion injury is believed to contribute to many important pathological conditions, including acute myocardial infarction, stroke, shock, and acute respiratory distress syndrome [24].

Therapies aimed at blocking the entry of neutrophils into tissues are being evaluated as possible new strategies for these serious disorders[25].

Th1 inflammation is characterized by tissue infiltration of interferon-γ CD4 + and CD8 + secretory effector T cells and activated macrophages. This type of cell-mediated inflammatory response is thought to play an important pathophysiological role in a multitude of prominent human diseases, including type 1 diabetes mellitus, CD [26], multiple sclerosis, RA, atherosclerosis, psoriasis, and solid organ allograft rejection. Interfering with the trafficking of molecules in Th1 cells and activated macrophages will have the advantage of being potentially beneficial in many of the aforementioned disorders [27]. In fact, the inhibition of integrin αL (CD11a), which together with CD18 forms the LFA-1 complex, has proven to be clinically promising with the use of odulimomab [28] for graft-versus-host-disease and transplant rejection and efalizumab for psoriasis [29]. In addition, natalizumab is very effective in CD and multiple sclerosis. However, blocking all α4-mediated leukocyte trafficking will lead to increased susceptibility to infection [30].

The challenge, then, is identifying the specific adhesion and signaling molecules that control the transport of these immune cells. Initially, it was thought that the CCR3 chemokine receptor was a molecule of this kind; however, subsequent studies have shown that, although expressed in all eosinophils, it is present only in a minority of Th2 cells[31]. Mice with CCR3 deficiency have a profound defect in eosinophil migration, but Th2 cell trafficking appears to be intact, and mice with CCR3 deficiency can generate a tissue-specific allergic response [32].

Therefore, CCR3 blocking is a feasible approach to blocking eosinophil transit, but not Th2 cell transit; Th2 cell transport is under the control of chemotactic receptors and genes inducible by the STAT6 transcription factor [33]. Therefore, Th1 cells use "preferably" CXCR3, CXCR6, and CCR5, whereas Th2 cells use "preferably" CCR4, CCR8, and the prostaglandin D2 receptor CRTH2. However, it remains to be determined whether the inhibition of these or other combinations of chemokine receptors specifically expressed in Th1 versus Th2 cells can selectively inhibit the transport of any type of T cell, either alone or in combination with integrin blocking therapy in patients with CD [34].

2.5. Main pathophysiological effects of Crohn's disease that may be triggered by a renal pathology

It generally is accepted that CD results from an aberrant immune response to commensal microflora in genetically susceptible individuals. However, the nature of immune defects, the microflora involved, and genetic susceptibility remain incompletely defined and controversial [35].

On the other hand, the most frequent renal complication in patients with CD is nephrolithiasis with an incidence of 4%–23% [36], followed by nephrotic syndrome [37] and 24-h urinary proteinuria > 10 g [38]. Kidney stone formation occurs in 12% of patients with CD [39].

Regarding the pathophysiological causes of CD with nephrotic syndrome, some researchers attribute it to an abnormal humoral immune response of Th2 or B cells, whereas some believe that CD is caused by a Th1 or Th17 immune reaction or an autoimmune abnormality [40], [41].

Additionally, the increased urinary excretion of orosomucoid (ORM, also called α-1 glycoprotein acid) has been described, which can provide a new biomarker in CD. One study has reported that U-ORM/u-CREAT values were seven times higher in children (0.50 vs 0.07 mg/mmol; $P < 0.001$) and two times higher in adults (0.32 vs 0.14 mg/mmol; $P = 0.01$) with active CD than in patients with inactive disease. U-ORM/u-CREAT has shown good correlation with conventional inflammatory markers (hs-CRP, serum ORM; $P < 0.01$) and activity indices (HBI, $P = 0.018$; PCDAI, $P < 0.001$). Furthermore, U-ORM/u-CREAT has a discriminative performance similar to those of hs-CRP and serum ORM in the differentiation of active and inactive CD in pediatric patients[42].

2.6. Pathological characteristics of amyloidosis in Crohn's disease

Amyloidosis is one of the complications that may occur in patients with CD. Some unusual characteristics of both amyloidosis and CD in these patients include the relatively advanced age of patients with CD but relatively young age of those with amyloidosis and the high incidence of colon involvement in the former. In addition, recurrent polychondritis, seronegative RA, and cutaneous vasculitis, which are not fortuitously associated with amyloidosis, can be observed in patients with CD, with mainly CD with colon involvement observed in cases of seronegative RA and cutaneous vasculitis. The frequent associations of CD with pyoderma gangrenosum are also worth noting [43].

All of these systemic, skin, or gastrointestinal tract disorders associated with amyloidosis are characterized by tissue damage with inflammatory infiltrates, without clear evidence of an autoimmune mechanism, which could be part of an abnormal immune response against connective tissue components or infectious agents. It is also worth noting that a nonfortuitous association has been suggested between CD and amyloidosis [43].

Acceleration of Amyloidosis by Inflammation is unclear but there is information that T helper 17 (Th17) cells, defined by RORγt-dependent production of IL-17A and IL-17F, exert homeostatic functions in the gut upon microbiota-directed differentiation from naive CD4+ T cells. In the non-pathogenic setting, their cytokine production is regulated by serum amyloid A proteins (SAA1 and SAA2) secreted by adjacent intestinal epithelial cells. However, Th17 cell behaviors vary markedly according to their environment[44].
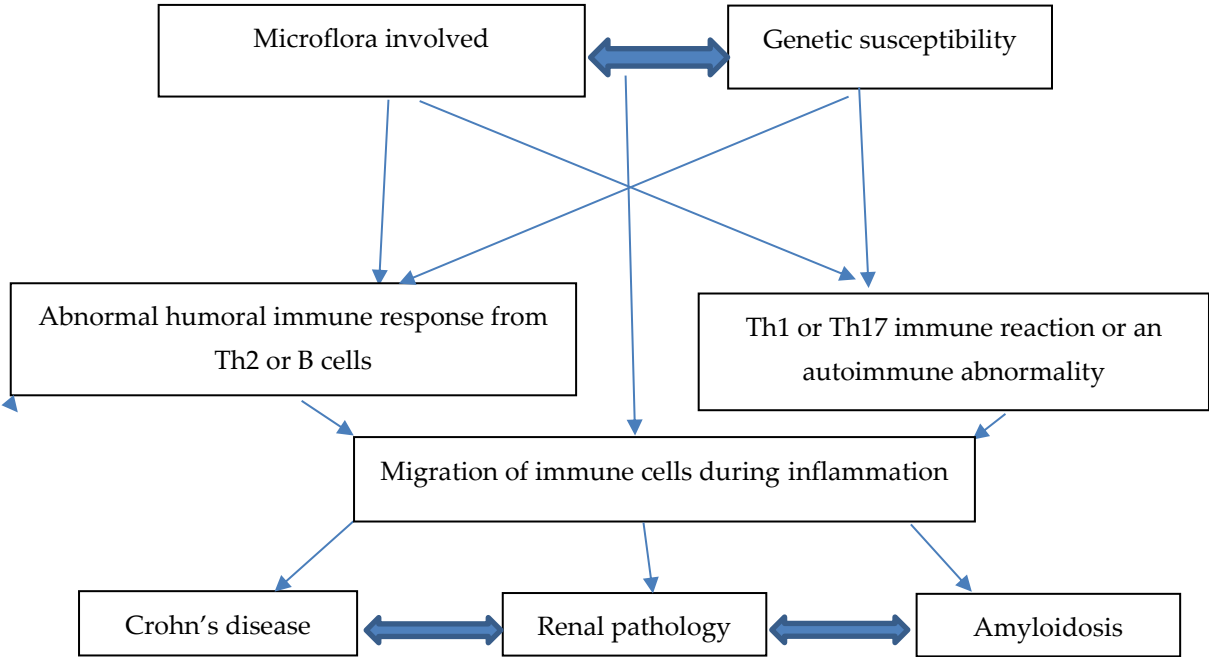
Figure 2. Pathological associations between CD and other complications such as amyloidosis and renal disease

3. Conclusions

The association between renal pathological abnormalities and CD found within the spectrum of nephrotic syndrome to nephrolithiasis is variable; moreover, the underlying mechanisms that trigger renal pathologies in patients with CD remain debatable. However, they can be grouped into abnormal humoral immune response of Th2 or B cells and alterations in the migration mechanism of immune cells during inflammation in patients with CD.

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